SANITIZED VERSION

8EHQ-1202-15240

November 25, 2002



Document Processing Center (TS-790)
ATTN: Section 8(e) Coordinator
Office of Toxic Substances
Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460

**CONTAINS CONFIDENTIAL BUSINESS INFORMATION**

COMPANY SANITIZED

Dear Sir or Madam:

This notice is being submitted in accordance with TSCA Section 8(e). Pursuant to discussions on October 8, 2002, with [redacted] is submitting the attached Robust Summary for Tri-(2-ethylhexyl) Trimellitate, CAS Registry Number 3319-31-1. from a combined prenatal and postnatal developmental toxicity study. Please contact [redacted], should you have any questions regarding this matter.

Confidentiality Statement

This letter contains confidential business information. These claims are pursuant to §14 of TSCA and to 40 CFR Part 2. All information claimed as confidential is boxed and a sanitized version of this letter is provided. No public disclosure may be made of information in this letter that has been claimed confidential absent prior notification to [redacted] pursuant to 40 CFR Part 2.

Response to the questions in the document entitled "Substantiating Claims of Confidentiality" are given below:

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[redacted]

If you have any questions concerning this notice, please contact [redacted].

Sincerely,

[redacted]

## DEVELOPMENTAL TOXICITY/TERATOGENICITY SANITIZED VERSION

### TEST SUBSTANCE

- Identity: Tri-(2-ethylhexyl) Trimellitate (TEHTM), CAS Registry number 3319-31-1, purity 98.93% (by GC).

### METHOD

- Method/guideline: Teratological Evaluation (modified by extension)
- Type: Pre- and postnatal developmental toxicity evaluation
- GLP: Yes
- Year (study performed): 2000-2001
- Species: Rat
- Strain: Sprague-Dawley
- Route of administration: oral (gavage)
- Doses/concentration levels: 0, 100, 500, 1050 mg/kg
- Sex: Female
- Exposure period: Gestation days 6-19 (prenatal teratology evaluation),and gestation day 6 though to lactation day 20 (postnatal development evaluation)
- Frequency of treatment: Daily, except day of parturition for animals allowed to litter
- Control group and treatment: corn oil
- Post-exposure observation period: 12 weeks (male offspring), or 3 weeks (female offspring)
- Number of animals: 35 per dose group
- Statistical methods: ANOVA followed by William's test, or Kruskal-Wallis/Hollander & Wolfe followed by Shirley's test, Steel's test, Cochran-Armitage, Fisher's exact test.
- Remarks:
  - Dams were sacrificed one day prior to parturition (n=20 per dose group) for teratologic evaluation, or after weaning of the offspring (n=15 per dose group).
  - Anogenital distance was measured in all fetuses prior to preparation for skeletal assessment or serial sectioning.
  - All viable offspring were maintained without treatment to 6 (females) or 15 (males) weeks of age, to determine the effects of exposure to TEHTM *in utero* and during lactation on sexual maturation and the reproductive tract.
  - Offspring were assessed for auditory startle response and pupil reaction to light on postnatal day (PND) 20
  - On PND13/14, males were examined for the presence of abdominal and thoracic areolae. Any animals with areolae were subsequently re-examined at PND18.
  - Females were examined for the timing of vaginal opening and males for the timing of preputial separation.
  - At necropsy, particular attention was paid to the morphology of reproductive tract organs in offspring of both sexes. Organs from males were also weighed.
  - Testes were fixed and examined microscopically (only left testis examined in 100 and 500 mg/kg/d TEHTM groups).

### RESULTS

- NOAEL (NOEL) maternal toxicity: 1050mg/kg/d
  No significant effects were detected in bodyweight or gravid uterus weight at any dose level, either during gestation or lactation. There were no differences between the groups with reference to the number of implantations, post-implantation loss, gestation length and index, or (live) litter size.
- NOAEL (NOEL) prenatal developmental toxicity: 1050mg/kg/d

No significant differences in fetal body weights were detected between the treated and control groups. No significant variations or malformations were observed in gross external appearance, viscera, skeletal system, or anogenital distance.

- NOAEL postnatal evaluation of offspring: 1050mg/kg/d
  There were no significant differences between control and treatment groups for offspring survival, sex ratio, bodyweight or bodyweight gain, auditory startle and pupil closure responses, age at vaginal opening or preputial separation. At necropsy, there were no effects attributable to treatment in either females (6 weeks of age) or males (15 weeks of age), that is morphology of the (male and female) reproductive tract organs, weight of the reproductive tract organs (males only assessed), or testis histopathology.
- NOEL postnatal evaluation of offspring: 500mg/kg/d. LOEL: 1050mg/kg/d
  There was a slight increase ($P<0.05$) in the number of male animals with retained areolar regions at PND13 at 1050mg/kg/d, but the affected animals only had one or two more sites than those in the control group. The areolae present at PND13 were no longer present on re-examination at PND18.

**Percentage of pups in each group with retained areolar regions at PND13.**

| Number of areolae per pup | Dose TEHTM (mg/kg/d) | | | |
|---|---|---|---|---|
| | 0 | 100 | 500 | 1050 |
| 0 | 97.9 | 97.1 | 98.2 | 89.1 |
| 1 | 1.0 | 1.0 | 0.9 | 5.4 |
| 2 | 0.0 | 0.0 | 0.0 | 4.3 |
| 3 | 0.0 | 0.0 | 0.0 | 0.0 |
| 4 | 1.0 | 1.9 | 0.9 | 1.1 |
| Total retention | 2.1 | 2.9 | 1.8 | 10.9 |

There was a higher incidence of displaced testes in fetuses of the 1050mg/kg/d dose group in comparison to the concurrent control, although the incidence was within the range of recent historical control data for this endpoint. No displaced testes were noted in any of the fetuses undergoing less rigorous examination prior to preparation for skeletal examination. There was no difference in the incidence of non-scrotal testes between males of treatment and control groups at 15 weeks of age.

The incidence of renal cavitation was higher than concurrent control in fetuses that were macroscopically assessed prior to skeletal examination, but this finding was within the range of recent historical control values, and was not repeated during examination of fetuses by the more rigorous serial sectioning technique.

| Endpoint | Incidence (number pups/litters affected) | | | | |
|---|---|---|---|---|---|
| | Dose TEHTM (mg/kg/d) | | | | Historical control range |
| | 0 | 100 | 500 | 1050 | |
| Displaced testes* | 4(3) | 3(3) | 3(3) | 9(6) | 2(2) – 10(9) |
| Displaced testes** | 0(0) | 0(0) | 0(0) | 0(0) | |
| Renal cavitation* | 0(0) | 0(0) | 0(0) | 0(0) | |
| Renal cavitation** | 1(1) | 6(4) | 7(5) | 9(5) | 3(1) – 9(5) |
| Hydroureter | 0(0) | 4(3) | 5(3) | 6(5) | 3(2) – 9(4) |

* fetuses examined for visceral abnormalities by Wilson's serial sectioning technique
** fetuses examined for visceral abnormalities prior to skeletal

The incidence of renal dilatation in males at 15 weeks of age was significantly increased in animals of the 500 and 1050mg/kg/d treatment groups. However, the incidence in the concurrent control (1.0%) was lower than that in five previous studies, and that in the highest treatment group was lower than the control value in three previous studies.

| Endpoint | Incidence (% males affected) | | | | |
|---|---|---|---|---|---|
| | Dose TEHTM (mg/kg/d) | | | | Historical control range |
| | 0 | 100 | 500 | 1050 | |
| Renal cavitation | 1.0 | 3.8 | 7.0 | 13.2 | 3.6-22.2 |

## CONCLUSIONS

- No treatment-related effects were observed in maternal, fetal, or offspring body weights, or litter viability. No teratogenic effects were observed, nor were there any effects upon sexual maturation or development of the reproductive tract in male or female offspring. The only statistically significant finding was a slight increase in the number of areolar regions on the abdomen of male offspring at PND13, which was not seen at PND18. However, in the absence of any other supporting data, this finding is of questionable toxicological significance.

  Apparent increases in the incidence of displaced testis (fetuses), renal cavitation (fetuses, 15 week old males), and hydroureter (fetuses) appear to be related to the low incidence of these findings in the concurrent control group compared to the range of historical control values. Not only were the incidences of these findings in the TEHTM-treated groups within the range of historical controls from recent studies at the same laboratory, they were not supported by complimentary observations made in fetuses or offspring. They are therefore not considered to be related to treatment.

## DATA QUALITY

Reliability: Klimisch Code = 1, reliable without restrictions

## REFERENCES

- Huntingdon Life Sciences Ltd (2002). TEHTM Study for Effects on Embryo-Fetal and Pre- and Post-Natal Development in CD Rat by Oral Gavage Administration.

## OTHER